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(54) Title: SELECTIVE NOREPINEPHRINE SEROTONIN REUPTAKE INHIBITORS FOR TREATING FIBROMYALGIA SYNDROME, CHRONIC FATIQUE SYNDROME AND PAIN

(57) Abstract: The present invention provides a method of treating, in a mammal, chronic fatigue syndrome (CFS), chronic fatigue syndrome (CFS) that is associated with depression, a combination of chronic fatigue syndrome (CFS) and fibromyalgia syndrome (FMS), fibromyalgia syndrome (FMS) associated with depression, pain and pain associated with depression. The method includes administering a therapeutically effective amount of a dual serotonin norepinepbrine reuptake inhibitor compound or a pharmaceutically acceptable salt thereof.

SELECTIVE NOREPINEPHRINE SEROTONIN REUPTAKE INHIBITORS FOR TREATING FIBROMYALGIA SYNDROME, CHRONIC FATIQUE SYNDROME AND PAIN

FIELD OF THE INVENTION

The present invention relates to methods for the treatment of fibromyalgia syndrome, chronic fatigue syndrome, and pain. In particular, the present invention relates to methods of treating fibromyalgia syndrome, chronic fatigue syndrome, and pain with a sub-class of dual serotonin norepinephrine reuptake inhibitors that exhibit equal or greater inhibition of norepinephrine reuptake than serotonin reuptake.

BACKGROUND OF THE INVENTION

Fibromyalgia syndrome (FMS) is the most frequent cause of chronic, widespread pain, estimated to affect 2-4% of the population. FMS is characterized by a generalized heightened perception of sensory stimuli. Patients with FMS display abnormalities in pain perception in the form of both allodynia (pain with innocuous stimulation) and hyperalgesia (increased sensitivity to painful stimuli). The syndrome, as defined by the American College of Rheumatology's criteria, involves the presence of pain for over 3 months duration in all four quadrants of the body, as well as along the spine. In addition, pain is elicited at 11 out of 18 "tender points" upon palpation. Other associated symptoms include fatigue, nonrestorative sleep, and memory difficulties.

Chronic fatigue syndrome (CFS) is a debilitating disorder characterized by profound tiredness or fatigue. Patients with CFS may become exhausted with only light physical exertion, and must often function at a level of activity substantially lower than their capacity before the onset of illness. In addition to the key defining characteristic of fatigue, CFS patients generally report various nonspecific symptoms, including weakness, muscle aches and pains, excessive sleep, malaise, fever, sore throat, tender lymph nodes, impaired memory and/or mental concentration, insomnia, and depression. Like patients with FMS, patients with CFS suffer from disordered sleep, localized tenderness, and complaints of diffuse pain and fatigue.

There are two widely used criteria for diagnosing CFS. The criteria established by the U.S. Centers for Disease Control and Prevention include medically unexplained fatigue of at least six months duration that is of new onset, not a result of ongoing exertion and not substantially alleviated by rest, and a substantial reduction in previous levels of activity. In addition, the diagnosis involves the determination of the presence of four or more of the following symptoms - subjective memory impairment, tender lymph nodes, muscle pain, joint pain, headache, unrefreshing sleep, and postexertional malaise (>24 hours). Reid et al., 2000, *British Medical Journal* 320: 292-296. The diagnostic criteria from Oxford includes severe, disabling fatigue of at least six months duration that

affects both physical and mental functioning and the fatigue being present for more than 50% of the time. In addition, the diagnosis involves the determination of the presence of other symptoms, particularly myalgia and sleep and mood disturbance. Reid et al., 2000, *British Medical Journal* 320: 292-296.

Owing to their common symptomology, FMS and CFS are thought to be related. However, they manifest different major symptoms. Whereas pain is the major symptom reported by patients with FMS, fatigue is the major symptom reported by patients with CFS. Given their relatedness, these two indications have been treated with the same medications. Some of the common medications currently employed to treat CFS and/or FMS include, but are not limited to, analgesics, hypnotics, immune suppressants, various other prescribed medications, and an array of non-prescription medications. Although a broad array of medications are used in FMS and CFS patients, no single pharmacological agent or combination of agents is effective in the treatment of either of these disorders. Thus, due to the lack of effective treatment regimens for FMS and/or CFS, there is a need to develop effective treatments.

Pain is associated with a variety of different underlying illnesses or injuries. Pain may be either acute or chronic. Chronic or intractable pain is often endured over many years or decades. Patients suffering from chronic pain often develop emotional

problems which can lead to depression and in the worst case, attempted suicide. Long lasting pain often occurs particularly in joints, in muscles, connective tissue and in the back. In the United States alone, chronic pain causes a loss of more than 250 million working days per year. A patient is considered to have chronic pain when complaints thereof last longer than six months. In the course of time, chronic pain may form an independent clinical syndrome.

Most analgesic agents in use today are not always effective, may produce serious side effects and can be addictive. Hence, there is a demand for more active analgesic agents with diminished side effects and toxicity, and which are non-addictive. The ideal analgesic would reduce the awareness of pain, produce analgesia over a wide range of pain types, act satisfactorily whether given orally or parenterally, produce minimal or no side effects, and be free from the tendency to produce tolerance and drug dependence.

SUMMARY OF THE INVENTION

In one aspect, the invention provides a method of treating fibromyalgia syndrome (FMS) and/or the symptoms associated therewith in an animal subject, including a human. The method generally involves administering to an animal subject suffering from FMS an effective amount of a dual serotonin norepinephrine reuptake inhibitor ("SNRI") compound of a specific type, or a pharmaceutically acceptable salt thereof. The SNRI compounds that are useful to treat FMS and/or

symptoms associated therewith are characterized by a non-tricyclic structure and inhibit the reuptake of norepinephrine to an equal or greater extent than they inhibit the reuptake of serotonin (referred to hereinafter as "NE 5-HT SNRI compounds"). In one embodiment of the invention, the NE 5-HT SNRI compound administered inhibits norepinephrine reuptake to a greater degree than it inhibits serotonin reuptake (referred to hereinafter as a "NE>5-HT SNRI compound"). One particular example of a such a NF>5-HT SNRI compound is milnacipran, or a pharmaceutically acceptable salt thereof. In another embodiment, the NE 5-HT SNRI compound is not administered adjunctively with phenylalanine, tyrosine and/or tryptophan.

In another aspect, the invention provides a method of treating pain in an animal subject, including a human. The method generally involves administering to an animal subject suffering from pain an effective amount of a NE 5-HT SNRI compound, or a pharmaceutically acceptable salt thereof. In one embodiment, a NE>5-HT SNRI compound is administered. One particular example of a NE>5-HT SNRI compound is milnacipran or a pharmaceutically acceptable salt thereof. In another embodiment, the NE 5-HT SNRI compound is not administered adjunctively with phenylalanine, tyrosine and/or tryptophan.

In still another aspect, the invention provides a method of treating CFS and/or symptoms associated therewith. The method generally involves

administering to a patient suffering from CFS an effective amount of a NE 5-HT SNRI compound, or a pharmaceutically acceptable salt thereof. In one embodiment, a NE>5-HT SNRI compound is administered. One particular example of a NE>5-HT SNRI compound is milnacipran or a pharmaceutically acceptable salt thereof. In another embodiment, the NE 5-HT SNRI compound is not administered adjunctively with phenylalanine, tyrosine and/or tryptophan.

In yet another aspect, the invention provides a kit comprising a NE 5-HT SNRI compound packaged in association with instructions teaching a method of using the compound according to one or more of the above-described methods. The kit can contain the NE 5-HT SNRI compound packaged in unit dosage form. In one embodiment, a NE>5-HT compound can be included in the kit. One particular example of a NE>5-HT SNRI compound is milnacipran or a pharmaceutically acceptable salt thereof.

In still another aspect, the invention provides a method of treating chronic fatigue syndrome (CFS) in a mammal, the method comprising administering to the mammal an effective amount of a selective norepinephrine (NE) - serotonin (5-HT) reuptake inhibitor (NSRI).

In still another aspect, the invention provides a method of treating, in a mammal, chronic fatigue syndrome (CFS) that is associated with depression, the method comprising administering to the mammal an

effective amount of a selective norepinephrine (NE) - serotonin (5-HT) reuptake inhibitor (NSRI).

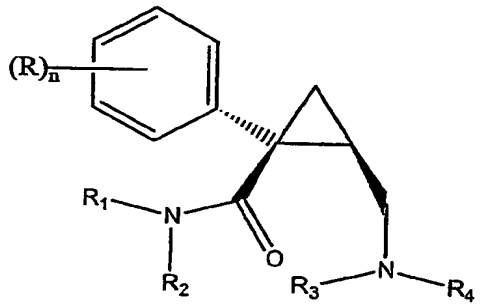
In still another aspect, the invention provides a method of treating, in a mammal, a combination of chronic fatigue syndrome (CFS) and fibromylagia syndrome (FMS), the method comprising administering to the mammal an effective amount of a selective norepinephrine (NE) - serotonin (5-HT) reuptake inhibitor (NSRI).

In still another aspect, the invention provides a method of treating, in a mammal, fibromylagia syndrome (FMS) associated with depression, the method comprising administering to the mammal an effective amount of a selective norepinephrine (NE) - serotonin (5-HT) reuptake inhibitor (NSRI).

In still another aspect, the invention provides a method of treating pain in a mammal, the method comprising administering to the mammal an effective amount of a selective norepinephrine (NE) - serotonin (5-HT) reuptake inhibitor (NSRI).

In still another aspect, the invention provides a method of treating, in a mammal, pain associated with depression, the method comprising administering to the mammal an effective amount of a selective norepinephrine (NE) - serotonin (5-HT) reuptake inhibitor (NSRI).

In still another aspect, the invention provides a pharmaceutical composition comprising: (a) a pharmaceutically acceptable carrier and (b) an effective anti-chronic fatigue syndrome (CFS) amount, an anti-chronic fatigue syndrome (CFS) associated with depression amount, a dual anti-chronic fatigue syndrome (CFS) and anti-fibromylagia syndrome (FMS) amount, an anti-fibromylagia syndrome (FMS) associated with depression amount, an anti-pain amount, and/or an anti-pain associated with depression amount of a compound of formula (I):



(I)

or sterioisomeric forms, mixtures of sterioisomeric forms, or pharmaceutically acceptable salts thereof wherein,

R is independently hydrogen, halo, alkyl, substituted alkyl, alkoxy, substituted alkoxy, hydroxy, nitro, amino, or substituted amino;

n is 1 or 2;

R_1 and R_2 are each independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl,

substituted cycloalkyl, alkaryl, substituted alkaryl, heteroaryl, substituted heteroaryl, heterocycle, or substituted heterocycle; or

R_1 and R_2 can form a heterocycle, substituted heterocycle, heteroaryl, or substituted heteroaryl with the adjacent nitrogen atom;

R_3 and R_4 are each independently hydrogen, alkyl, or substituted alkyl; or

R_3 and R_4 can form a heterocycle, substituted heterocycle, heteroaryl, or substituted heteroaryl with the adjacent nitrogen atom.

In still another aspect, the invention provides a pharmaceutical composition comprising: (a) a pharmaceutically acceptable carrier and (b) an effective anti-chronic fatigue syndrome (CFS) amount, an anti-chronic fatigue syndrome (CFS) associated with depression amount, a dual anti-chronic fatigue syndrome (CFS) and anti-fibromylagia syndrome (FMS) amount, an anti-fibromylagia syndrome (FMS) associated with depression amount, an anti-pain amount, and/or an anti-pain associated with depression amount of milnacipran.

In still another aspect, the invention provides a pharmaceutical composition comprising: (a) a pharmaceutically acceptable carrier and (b) an effective anti-chronic fatigue syndrome (CFS) amount, an anti-chronic fatigue syndrome (CFS) associated with depression amount, a dual anti-chronic fatigue syndrome (CFS) and anti-fibromylagia syndrome (FMS)

amount, an anti-fibromylagia syndrome (FMS) associated with depression amount, an anti-pain amount, and/or an anti-pain associated with depression amount of milnacipran (about 25 mg/day to about 250 mg/day).

In still another aspect, the invention provides a pharmaceutical composition comprising: (a) a pharmaceutically acceptable carrier, (b) an effective anti-chronic fatigue syndrome (CFS) amount, an anti-chronic fatigue syndrome (CFS) associated with depression amount, a dual anti-chronic fatigue syndrome (CFS) and anti-fibromylagia syndrome (FMS) amount, an anti-fibromylagia syndrome (FMS) associated with depression amount, an anti-pain amount, and/or an anti-pain associated with depression amount of milnacipran, and (c) at least one of an antidepressant, an analgesic, a muscle relaxant, an anorectic, a stimulant, an antiepileptic drug, a sedative, and a hypnotic.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Abbreviations

CFS	chronic fatigue syndrome
FMS	fibromyalgia syndrome
5-HT	serotonin
NARIs	norepinephrine specific reuptake inhibitors
NE	norepinephrine
NMDA	N-methyl D-aspartate
NSAIDs	non-steroidal anti-inflammatory drugs
SSRIs	selective serotonin reuptake inhibitors
TCAs	tricyclic antidepressants

SNRIs dual serotonin norepinephrine reuptake inhibitors

Definitions

The term "dual serotonin norepinephrine reuptake inhibitor compound" or SNRI refers to the well-recognized class of anti-depressant compounds that selectively inhibit reuptake of both serotonin and norepinephrine. Common SNRI compounds include, but are not limited to, venlafaxine, duloxetine, and milnacipran.

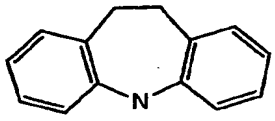
The terms "NE 5-HT SNRI" and "NE>5-HT SNRI" refer to particular subclasses of SNRI compounds that are useful in the methods and kits of the present invention, as will be described in more detail herein.

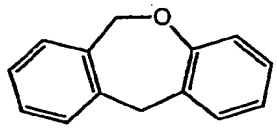
Treatment of FMS, CFS and/or Pain

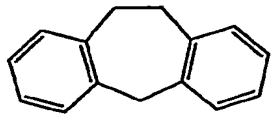
The present invention provides methods and kits for treating FMS, CFS, and pain. A particular subclass of SNRI compounds is useful for practicing the present invention. Compounds in this SNRI subclass, referred to as "NE 5-HT SNRI compounds," inhibit norepinephrine reuptake more than or equal to serotonin reuptake. Moreover, the NE 5-HT compounds of the invention exclude compounds that belong to the distinct class of antidepressant compounds commonly referred to in the art as tricyclic antidepressants or TCAs. In particular, compounds useful for practicing the present invention inhibit norepinephrine reuptake

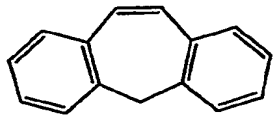
more than serotonin reuptake, referred to as "NE>5-HT SNRI compounds."

Tricyclic antidepressants (TCAs) are a well-recognized class of antidepressant compounds that are characterized by a dibenz[b,e]azepine (structure I), dibenz[b,e]oxepine (structure II), dibenz[a,d]cycloheptane (structure III) or dibenz[a,d]cycloheptene (structure IV) tricyclic ring structure. These various rings are depicted below:

(I) 

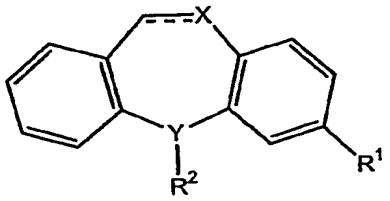
(II) 

(III) 

(IV) 

The TCAs are typically substituted at position 1 of the tricyclic ring with alkylamines or alkylidenamines, and may include additional substituents (typically on the benzo groups). Many common TCAs, including imipramine, desipramine,

clomipramine, trimipramine, amitriptyline, nortriptyline, doxepin, cyclobenzaprine and protriptline are characterized by the general formula (V), below:



(V)

wherein:

X is O or C;

Y is N or C;

R^1 is H or Cl;

R^2 is selected from the group consisting of $-(CH_2)_3N(CH_3)_2$, $-(CH_2)_3NHCH_3$, $-CH_2CH(CH_3)CH_2N(CH_3)_2$, $=CH(CH_2)N(CH_3)_2$, $=CH(CH_2)_2NHCH_3$ and $-(CH_2)_3NHCH_3$ and

the dotted line represents a single bond or a double bond.

The NE 5-HT SNRI compounds of the invention exclude compounds classified as tricyclic antidepressants, and thus exclude compounds characterized by the above-depicted fused tricyclic nuclei of structures (I), (II), (III), and (IV).

As mentioned above, the NE 5-HT SNRI compounds useful in the methods and kits of the invention include compounds that inhibit norepinephrine reuptake to a greater extent than serotonin reuptake, as well as compounds that inhibit the reuptake of these two

monoamines to an equivalent extent. In one embodiment of the invention, the NE 5-HT SNRI compounds have a ratio of inhibition of norepinephrine reuptake to serotonin reuptake ("NE:5-HT") in the range of about 1-100:1. In a particular embodiment, the compounds are NE>5-HT SNRI compounds, i.e., compounds that inhibit norepinephrine reuptake to a greater extent than serotonin reuptake. Such NE>5-HT SNRI compounds generally have a NE:5-HT in the range of about 1.1-100:1. That is, such NE>5-HT SNRI compounds are at least about 1.1 to about 100 times more effective at inhibiting norepinephrine reuptake than serotonin reuptake. NE>5-HT SNRI compounds having a NE:5-HT ratio in the range of about 2:1 to about 10:1 may be particularly effective.

Various techniques are known in the art to determine the NE:5-HT of a particular SNRI. In one embodiment, the ratio can be calculated from IC_{50} data for NE and 5-HT reuptake inhibition. For example, it has been reported that for milnacipran the IC_{50} of norepinephrine reuptake is 100 nM, whereas the IC_{50} serotonin reuptake inhibition is 200 nM. *See* Moret et al., 1985, *Neuropharmacology* 24(12):1211-1219; Palmier et al., 1989, *Eur J Clin Pharmacol* 37:235-238. Therefore, the NE:5-HT reuptake inhibition ratio for milnacipran based on this data is 2:1. Of course, other IC values such as IC_{25}, IC_{75}, etc. could be used, so long as the same IC value is being compared for both norepinephrine and serotonin. The concentrations necessary to achieve the desired degree of inhibition

(i.e., IC value) can be calculated using known techniques either *in vivo* or *in vitro*. *See* Sanchez et al., 1999, *Cellular and Molecular Neurobiology* 19(4):467-489; Turcotte et al., 2001, *Neuropsychopharmacology* 24(5):511-521; Moret et al., 1985, *Neuropharmacology* 24(12):1211-1219; Moret et al., 1997, *J. Neurochem.* 69(2):815-822; Bel et al., 1999, *Neuropsychopharmacology* 21(6):745-754; and Palmier et al., 1989, *Eur J Clin Pharmacol* 37:235-238.

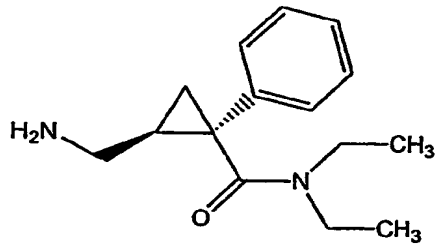
The NE:5-HT of a particular SNRI also can be calculated using equilibrium dissociation constants (K_D's) for norepinephrine and serotonin transporters as described in Tatsumi et al., 1997, *European Journal of Pharmacology* 340:249-258. For example, a NE>5-HT SNRI compound with a K_D of 2 nM for the norepinephrine transporter and a K_D of 8 nM for the serotonin transporter has an NE:5-HT of 4:1.

Yet another means for determining the NE:5-HT of a particular SNRI involves measuring the affinity (K_i) of the SNRI for the norepinephrine and serotonin transporters as described in Owens et al., 1997, *JPET* 283:1305-1322. For example, a NE>5-HT SNRI compound with a K_i of 1 nM for the norepinephrine transporter and a K_i of 20 nM for the serotonin transporter has an NE:5-HT of 20:1.

A specific example of a NE 5-HT SNRI compound that can be used to practice the present invention is milnacipran. Additional NE 5-HT SNRI compounds that

can be used to practice the present invention include, by way of example and not limitation, any of the aminocyclopropane derivatives disclosed in the following references that inhibit norepinephrine reuptake to an equivalent or greater extent than serotonin reuptake (i.e., that have a NE:5-HT ratio that is 1:1): WO95/22521; U.S. Patent No. 5,621,142; Shuto et al., 1995, *J. Med. Chem.* 38:2964-2968; Shuto et al., 1996, *J. Med. Chem.* 39:4844-4852; Shuto et al., 1998, *J. Med. Chem.* 41:3507-3514; Shuto et al., 2001, *Jpn. J. Pharmacol.* 85:207-213; Noguchi et al., 1999, *Synapse* 31:87-96; and U.S. Patent No. 4,478,836. All of these references are hereby incorporated herein by reference in their entireties.

In a specific embodiment of the invention, the NE>5-HT compound is milnacipran. The chemical structure of milnacipran, cis-(±)-2-(aminomethyl)-N,N-diethyl-1-phenyl-yclopropanecarboxamide, is as follows:



Milnacipran is also known in the art as F2207, TN-912, dalcipran, midalcipran, and midalipran. The NE:5-HT of milnacipran is 2:1. *See* Moret et al., 1985, *Neuropharmacology* 24(12):1211-1219; Palmier et al., 1989, *Eur J Clin Pharmacol* 37:235-238. Milnacipran

and methods for its synthesis are described in U.S. Patent 4,478,836, which is hereby incorporated by reference in its entirety. Additional information regarding milnacipran may be found in the Merck Index, 12th Edition, at entry 6281. Quite significantly, milnacipran has been used as an antidepressant in approximately 400,000 patients, and is known to be non-toxic in humans. In clinical trials at dosages of 100 mg/day or 200 mg/day, milnacipran was well tolerated and usually produced no more adverse effects than placebo (Spencer and Wilde, 1998, *Drugs* 56(3):405-427).

Those of skill in the art will recognize that NE 5-HT SNRI compounds such as milnacipran may exhibit the phenomena of tautomerism, conformational isomerism, geometric isomerism and/or optical isomerism. It should be understood that the invention encompasses any tautomeric, conformational isomeric, optical isomeric and/or geometric isomeric forms of the NE 5-HT SNRI compounds having one or more of the utilities described herein, as well as mixtures of these various different forms. For example, as is clear from the above structural diagram, milnacipran is optically active. It has been reported in the literature that the dextrogyral enantiomer of milnacipran is about twice as active in inhibiting norepinephrine and serotonin reuptake than the racemic mixture, and that the levrogyral enantiomer is much less potent (see, e.g., Spencer and Wilde, 1998, *supra*; Viazzo et al., 1996, *Tetrahedron Lett.*

37(26):4519-4522; Deprez et al., 1998, *Eur. J. Drug Metab. Pharmacokinet.* 23(2):166-171). Accordingly, milnacipran may be administered in entantiomerically pure form (*e.g.*, the pure dextrogyral enantiomer) or as a mixture of dextogyral and levrogyral enantiomers, such as a racemic mixture. Unless specifically noted otherwise, the term "milancipran" as used herein refers to both enantiomerically pure forms of milnacipran as well as to mixtures of milnacipran enantiomers. Methods for separating and isolating the dextro- and levrogyral enantiomers of milnacipran and other NE 5-HT SNRI compounds are well-known (see, e.g., Grard et al., 2000, Electrophoresis 2000 21:3028-3034).

It will also be appreciated that in many instances the NE 5-HT SNRI compounds may metabolize to produce active NE 5-HT SNRI compounds. The use of active metabolites is also within the scope of the present invention.

It has been reported that milnacipran and its derivatives have antagonistic properties at the NMDA receptor. See Shuto et al., 1995, *J. Med. Chem.* 38:2964-2968; Shuto et al., 1996, *J. Med. Chem.* 39:4844-4852; Shuto et al., 1998, *J. Med. Chem.* 41:3507-3514; and Shuto et al., 2001, *Jpn. J Pharmacol.* 85:207-213. As a consequence, one particularly useful embodiment of the invention includes NE 5-HT SNRI compounds that also have NMDA antagonistic properties. The NE 5-HT SNRI compounds

with NMDA receptor antagonistic properties can have IC_{50} values from about 1 nM - 100 μM. For example, milnacipran has been reported to have an IC_{50} value of about 6.3 μM. The NMDA receptor antagonistic properties of milnacipran and its derivatives are described in Shuto et al., 1995, *J. Med. Chem.*, 38:2964-2968; Shuto et al., 1996, *J. Med. Chem.* 39:4844-4852; Shuto et al., 1998, *J. Med. Chem.* 41:3507-3514; and Shuto et al., 2001, *Jpn. J Pharmacol.* 85:207-213. Methods for determining the antagonism and affinity for antagonism are disclosed in Shuto et al., 1995, *J. Med. Chem.* 38:2964-2968; Shuto et al., 1996, *J. Med. Chem.* 39:4844-4852; Shuto et al., 1998, *J. Med. Chem.* 41:3507-3514; Noguchi et al., 1999, *Synapse* 31:87-96; and Shuto et al., 2001, *Jpn. J. Pharmacol.* 85:207-213. Aminocyclopropane derivatives disclosed in WO95/22521; U.S. Patent No. 5,621,142; Shuto et al., 1995, *J. Med. Chem.* 38:2964-2968; Shuto et al., 1996, *J. Med. Chem.* 39:4844-4852; Shuto et al., 1998, *J. Med. Chem.* 41:3507-3514; Noguchi et al., 1999, *Synapse* 31:87-96; and Shuto et al., 2001, *Jpn. J. Pharmacol.* 85:207-213 that inhibit NE reuptake equal to or greater than 5-HT reuptake and have NMDA antagonistic properties can be used to practice the present invention. These references are hereby incorporated by reference in their entirety.

It has recently been reported that compounds that inhibit reuptake of both NE and 5-HT, such as venlafaxine, duloxetine, milnacipran, and certain TCAs, are effective for the treatment of pain, CFS and

FMS, among other maladies, when administered in combination with neurotransmitter precursors such as phenylalanine, tyrosine and/or tryptophan. *See* WO 01/26623. For example, according to one study reported in WO 01/26623, a patient experiencing, *inter alia*, fatigue and fibromyalgia, was administered many types of drugs, including many types of non-steroidal anti-inflammatories, both tricyclic and serotonin reuptake inhibiting and noradrenalin reuptake inhibiting antidepressants, and even steroids, without effect. When given a combination of lofepramine (70 mg. bd) and L-phenylalanine (500 mg bd), the patient experienced a considerable improvement in fatigue and fibromyalgia, which persisted for more than six months. Thus, a compound that inhibits reuptake of both NE and 5-HT was effective only when administered in combination with a neurotransmitter precursor.

Quite surprisingly, the present inventors have discovered that the NE 5-HT SNRI subclass of SNRI compounds are effective in treating CFS, FMS and pain when administered alone (or in combination with other compounds that are not neurotransmitter precursors such as phenylalanine, tyrosine and/or tryptophan, as will be discussed in more detail, below). Thus, in one embodiment of the invention, the NE 5-HT SNRI compound is administered alone, or in combination with a compound other than a neurotransmitter precursor such as phenylalanine, tyrosine and/or tryptophan.

The NE 5-HT SNRI compounds, such as, for example, milnacipran, can be administered adjunctively with other active compounds such as antidepressants, analgesics, muscle relaxants, anorectics, stimulants, antiepileptic drugs, and sedative/hypnotics. Specific examples of compounds that can be adjunctively administered with the NE 5-HT SNRI compounds include, but are not limited to, neurontin, pregabalin, pramipexole, 1-DOPA, amphetamine, tizanidine, clonidine, tramadol, morphine, tricyclic antidepressants, codeine, cambamazepine, sibutramine, amphetamine, valium, trazodone and combinations thereof. Typically for FMS patients the NE 5-HT SNRI compounds may be adjunctively administered with antidepressants, anorectics, analgesics, antiepileptic drugs, muscle relaxants, and sedative/hypnotics. For CFS patients, the NE 5-HT SNRI compounds may be adjunctively administered antidepressants, anorectics, stimulants, and sedative/hypnotics. For patients suffering from pain the NE 5-HT SNRI compounds may be adjunctively administered with antidepressants, analgesics, antiepileptic drugs. By adjunctive administration is meant simultaneous administration of the compounds, in the same dosage form, simultaneous administration in separate dosage forms, and separate administration of the compounds. For example, milnacipran can be simultaneously administered with valium, wherein both milnacipran and valium are formulated together in the same tablet. Alternatively, milnacipran could be simultaneously administered with valium, wherein both the milnacipran

and valium are present in two separate tablets. In another alternative, milnacipran could be administered first followed by the administration of valium, or vice versa.

The NE 5-HT SNRI compounds can be administered therapeutically to achieve a therapeutic benefit or prophylactically to achieve a prophylactic benefit. By therapeutic benefit is meant eradication or amelioration of the underlying disorder being treated, e.g., eradication or amelioration of the underlying FMS, CFS or pain disorder, and/or eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder such that the patient reports an improvement in feeling or condition, notwithstanding that the patient may still be afflicted with the underlying disorder. For example, administration of milnacipran to a patient suffering from FMS provides therapeutic benefit not only when the underlying FMS indication is eradicated or ameliorated, but also when the patient reports decreased fatigue, improvements in sleep patterns, and/or a decrease in the severity or duration of pain.

Although depression is often comorbid in patients suffering from FMS and CFS, and could therefore be characterized as a symptom associated with these disorders, it is well-recognized in the art that NE 5-HT SNRI compounds such as milnacipran are useful in the treatment of depression. Accordingly, while successful treatment regimens of the invention

contemplate providing an improvement in at least one symptom associated with FMS or CFS, treatment regimens that cause an improvement only in depression are considered ineffective for purposes of the present invention. While improvements in associated psychological symptoms such as depression may be reported, for purposes of the present invention, an improvement in the underlying disorder and/or in at least one of the physiological symptoms associated with the disorder must be reported. Thus, the present invention does not contemplate the treatment of depression alone.

For therapeutic administration, the NE 5-HT SNRI compound typically will be administered to a patient already diagnosed with the particular indication being treated.

For prophylactic administration, the NE 5-HT SNRI compound may be administered to a patient at risk of developing FMS, CFS, or pain or to a patient reporting one or more of the physiological symptoms of FMS or CFS, even though a diagnosis of FMS or CFS may not have yet been made. Alternatively, prophylactic administration may be applied to avoid the onset of the physiological symptoms of the underlying disorder, particularly if the symptom manifests cyclically. In this latter embodiment, the therapy is prophylactic with respect to the associated physiological symptoms instead of the underlying indication. For example, the NE 5-HT SNRI compound could be prophylactically

administered prior to bedtime to avoid the sleep disturbances associated with FMS or CFS. Alternatively, the NE 5-HT SNRI compound could be administered prior to recurrence of pain, or prior to onset of fatigue.

While the invention has been described so far with respect to NE 5-HT SNRI compounds, the present invention can also be practiced with norepinephrine specific reuptake inhibitors (NARIs). NARIs are a well-recognized class of compounds that specifically inhibit the reuptake of only norepinephrine. An example of a compound that is classified as a NARI is reboxetine.

Specific embodiments of the present invention are provided below:

[1] One embodiment of the present invention provides a method of treating fibromyalgia syndrome (FMS) and/or physiological symptoms associated therewith in an animal subject, comprising administering to an animal subject suffering from FMS, an effective amount of milnacipran, or a pharmaceutically acceptable salt thereof.

[2] Another embodiment of the present invention provides the method according to embodiment [1], wherein the milnacipran is not administered adjunctively with phenylalanine, tyrosine or tryptophan.

[3] Another embodiment of the present invention provides the method according to embodiment [1], wherein FMS is treated.

[4] Another embodiment of the present invention provides the method according to embodiment [1], wherein symptoms associated with FMS are treated.

[5] Another embodiment of the present invention provides the method according to embodiment [1], wherein the compound is adjunctively administered with antidepressants, analgesics, muscle relaxants, anorectics, stimulants, antiepileptic drugs, sedatives, or hypnotics.

[6] Another embodiment of the present invention provides the method according to embodiment [1], wherein the compound is adjunctively administered with neurontin, pregabalin, pramipexole, 1-DOPA, amphetamine, tizanidine, clonidine, tramadol, morphine, codeine, carbamazepine, sibutramine, amphetamine, valium, or trazodone.

[7] Another embodiment of the present invention provides the method according to embodiment [1], wherein the animal subject is a human.

[8] Another embodiment of the present invention provides the method according to embodiment [1],

wherein the amount administered is from about 25 mg to about 400 mg per day.

[9] Another embodiment of the present invention provides the method according to embodiment [1], wherein the milnacipran is formulated in a sustained release dosage formulation.

[10] Another embodiment of the present invention provides a method of treating pain in an animal subject, comprising administering to an animal subject suffering from pain, an effective amount of milnacipran, or a pharmaceutically acceptable salt thereof.

[11] Another embodiment of the present invention provides the method according to embodiment [10], wherein the milnacipran is not administered adjunctively with phenylalanine, tyrosine or tryptophan.

[12] Another embodiment of the present invention provides the method according to embodiment [10], wherein the compound is adjunctively administered with antidepressants, analgesics, muscle relaxants, anorectics, stimulants, antiepileptic drugs, sedatives, or hypnotics.

[13] Another embodiment of the present invention provides the method according to embodiment [10], wherein the compound is adjunctively administered with

neurontin, pregabalin, pramipexole, l-DOPA, amphetamine, tizanidine, clonidine, tramadol, morphine, a tricyclic antidepressant, codeine, carbamazepine, sibutramine, amphetamine, valium, or trazodone.

[14] Another embodiment of the present invention provides the method according to embodiment [10], wherein the animal subject is a human.

[15] Another embodiment of the present invention provides the method according to embodiment [10], wherein the amount administered is from about 25 mg to about 400 mg per day.

[16] Another embodiment of the present invention provides the method according to embodiment [10], wherein the compound is formulated in a sustained release dosage formulation.

[17] Another embodiment of the present invention provides a method of treating chronic fatigue syndrome (CFS) and/or physiological symptoms associated therewith in an animal subject, comprising administering to an animal subject suffering from CFS, an effective amount of milnacipran, or a pharmaceutically acceptable salt thereof.

[18] Another embodiment of the present invention provides the method according to embodiment [17], wherein the milnacipran is not administered

adjunctively with phenylalanine, tyrosine or tryptophan.

[19] Another embodiment of the present invention provides the method according to embodiment [17], wherein the compound is adjunctively administered with antidepressants, analgesics, muscle relaxants, anorectics, stimulants, antiepileptic drugs, sedatives, or hypnotics.

[20] Another embodiment of the present invention provides the method according to embodiment [17], wherein the compound is adjunctively administered with neurontin, pregabalin, pramipexole, l-DOPA, amphetamine, tizanidine, clonidine, tramadol, morphine, a tricyclic antidepressant, codeine, carbamazepine, sibutramine, amphetamine, valium, or trazodone.

[21] Another embodiment of the present invention provides the method according to embodiment [17], wherein the animal subject is a human.

[22] Another embodiment of the present invention provides the method according to embodiment [17], wherein the amount administered is from about 25 mg to about 400 mg per day.

[23] Another embodiment of the present invention provides the method according to embodiment [17],

wherein the compound is formulated in a sustained release dosage formulation.

[24] Another embodiment of the present invention provides a kit comprising a milnacipran or a pharmaceutically acceptable salt thereof and instructions teaching a method of use according to any one of embodiments [1], [10] or [17].

[25] Another embodiment of the present invention provides the kit of embodiment [24] in which the milnacipran or salt thereof is packaged in unit dosage form.

Additional specific embodiments of the present invention are provided below.

[26] Another embodiment of the present invention provides a method of treating chronic fatigue syndrome (CFS) in a mammal, the method comprising administering to the mammal an effective amount of a selective norepinephrine (NE) - serotonin (5-HT) reuptake inhibitor (NSRI).

[27] Another embodiment of the present invention provides a method of treating, in a mammal, chronic fatigue syndrome (CFS) that is associated with depression, the method comprising administering to the mammal an effective amount of a selective norepinephrine (NE) - serotonin (5-HT) reuptake inhibitor (NSRI).

[28] Another embodiment of the present invention provides a method of treating, in a mammal, a combination of chronic fatigue syndrome (CFS) and fibromylagia syndrome (FMS), the method comprising administering to the mammal an effective amount of a selective norepinephrine (NE) - serotonin (5-HT) reuptake inhibitor (NSRI).

[29] Another embodiment of the present invention provides a method of treating, in a mammal, fibromylagia syndrome (FMS) associated with depression, the method comprising administering to the mammal an effective amount of a selective norepinephrine (NE) - serotonin (5-HT) reuptake inhibitor (NSRI).

[30] Another embodiment of the present invention provides a method of treating pain in a mammal, the method comprising administering to the mammal an effective amount of a selective norepinephrine (NE) - serotonin (5-HT) reuptake inhibitor (NSRI).

[31] Another embodiment of the present invention provides a method of treating, in a mammal, pain associated with depression, the method comprising administering to the mammal an effective amount of a selective norepinephrine (NE) - serotonin (5-HT) reuptake inhibitor (NSRI).

[32] Another embodiment of the present invention provides the method of any one of embodiments [26]-[31] wherein the mammal is a human.

[33] Another embodiment of the present invention provides the method of any one of embodiments [26]-[31] wherein the noradrenergic reuptake inhibitor (NARI) has an IC_{50} for inhibition of noradrenaline reuptake into synaptosomes from mammalian cerebral cortex of 1 micromolar (μM) or less.

[34] Another embodiment of the present invention provides the method of any one of embodiments [26]-[31] wherein the noradrenergic reuptake inhibitor (NARI) has an IC_{50} for inhibition of noradrenaline reuptake into synaptosomes from mammalian cerebral cortex of 100 nanomolar (nM) or less.

[35] Another embodiment of the present invention provides the method of any one of embodiments [26]-[31] wherein the selective NSRI has an NE : 5-HT reuptake inhibition ratio of at least about 1.

[36] Another embodiment of the present invention provides the method of any one of embodiments [26]-[31] wherein the selective NSRI has an NE : 5-HT reuptake inhibition ratio of up to about 20.

[37] Another embodiment of the present invention provides the method of any one of embodiments [26]-[31] wherein the selective NSRI has an NE : 5-HT

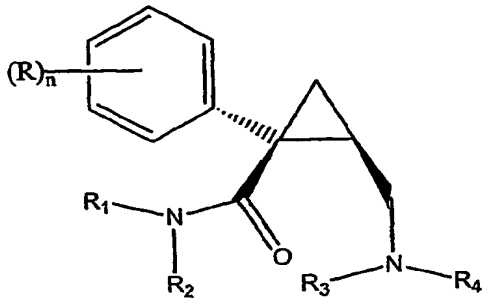
reuptake inhibition ratio of about 1 : 1 to about 20 : 1.

[38] Another embodiment of the present invention provides the method of any one of embodiments [26]-[31] wherein the selective NSRI has an NE : 5-HT reuptake inhibition ratio of about 1 : 1 to about 5 : 1.

[39] Another embodiment of the present invention provides the method of any one of embodiments [26]-[31] wherein the selective NSRI has an NE : 5-HT reuptake inhibition ratio of about 1 : 1 to about 3 : 1.

[40] Another embodiment of the present invention provides the method of any one of embodiments [26]-[31] wherein the selective norepinephrine (NE) - serotonin (5-HT) reuptake inhibitor (NSRI) has limited post-synaptic receptor effects, such that the K_i at each of adrenergic and cholinergic sites is greater than about 500 nanomolar (nM).

[41] Another embodiment of the present invention provides the method of any one of embodiments [26]-[31] wherein the compound is a compound of formula (I):



(I)

or a sterioisomeric form, a mixture of sterioisomeric forms, or a pharmaceutically acceptable salt thereof wherein,

R is independently hydrogen, halo, alkyl, substituted alkyl, alkoxy, substituted alkoxy, hydroxy, nitro, amino, or substituted amino;

n is 1 or 2;

R_1 and R_2 are each independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, alkaryl, substituted alkaryl, heteroaryl, substituted heteroaryl, heterocycle, or substituted heterocycle; or

R_1 and R_2 can form a heterocycle, substituted heterocycle, heteroaryl, or substituted heteroaryl with the adjacent nitrogen atom;

R_3 and R_4 are each independently hydrogen, alkyl, or substituted alkyl; or

R_3 and R_4 can form a heterocycle, substituted heterocycle, heteroaryl, or substituted heteroaryl with the adjacent nitrogen atom.

[42] Another embodiment of the present invention provides the method of embodiment [41] wherein R is hydrogen.

[43] Another embodiment of the present invention provides the method of embodiment [41] wherein n is 1.

[44] Another embodiment of the present invention provides the method of embodiment [41] wherein R_1 is alkyl.

[45] Another embodiment of the present invention provides the method of embodiment [41] wherein R_1 is ethyl.

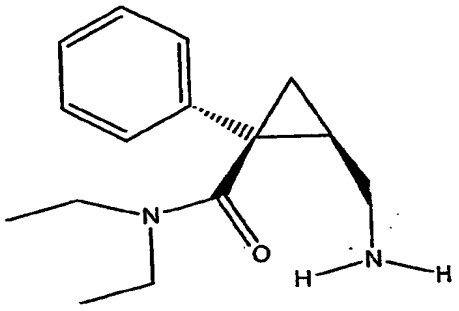
[46] Another embodiment of the present invention provides the method of embodiment [41] wherein R_2 is alkyl.

[47] Another embodiment of the present invention provides the method of embodiment [41] wherein R_2 is ethyl.

[48] Another embodiment of the present invention provides the method of embodiment [41] wherein R_3 is hydrogen.

[49] Another embodiment of the present invention provides the method of embodiment [41] wherein R_4 is hydrogen.

[50] Another embodiment of the present invention provides the method of embodiment [41] wherein the compound is (milnacipran) a compound of the formula:



or a sterioisomeric form, a mixture of sterioisomeric forms, or a pharmaceutically acceptable salt thereof.

[51] Another embodiment of the present invention provides the method of embodiment [50] wherein the compound of the formula recited therein (milnacipran) is administered up to about 400 mg/day.

[52] Another embodiment of the present invention provides the method of embodiment [50] wherein the compound of the formula recited therein (milnacipran) is administered in about 25 mg/day to about 250 mg/day.

[53] Another embodiment of the present invention provides the method of embodiment [50] wherein the compound of the formula recited therein (milnacipran) is administered one or more (e.g., 1, 2, 3, 4, or 5) times per day.

[54] Another embodiment of the present invention provides the method of any one of embodiments [26]-[28] wherein the chronic fatigue syndrome (CFS) is accompanied by the physiological symptoms selected from weakness, muscle aches and pains, excessive sleep, malaise, fever, sore throat, tender lymph nodes, impaired memory and/or mental concentration, insomnia, disordered sleep, localized tenderness, diffuse pain and fatigue, and combinations thereof.

[55] Another embodiment of the present invention provides the method of any one of embodiments [28]-[29] wherein the fibromylagia syndrome (FMS) is accompanied by the physiological symptoms selected from a generalized heightened perception of sensory stimuli, abnormalities in pain perception in the form of allodynia (pain with innocuous stimulation), abnormalities in pain perception in the form of hyperalgesia (increased sensitivity to painful stimuli), and combinations thereof.

[56] Another embodiment of the present invention provides the method of embodiment [29] wherein the fibromylagia syndrome (FMS) associated with depression comprises fibromylagia syndrome (FMS) and atypical depression.

[57] Another embodiment of the present invention provides the method of embodiment [29] wherein the fibromylagia syndrome (FMS) associated with depression comprises fibromylagia syndrome (FMS) and atypical

depression, and wherein the fibromylagia syndrome (FMS) precedes the atypical depression.

[58] Another embodiment of the present invention provides the method of embodiment [29] wherein the fibromylagia syndrome (FMS) associated with depression comprises fibromylagia syndrome (FMS) and atypical depression, and wherein the atypical depression precedes the fibromylagia syndrome (FMS).

[59] Another embodiment of the present invention provides the method of embodiment [31] wherein the pain associated with depression comprises atypical depression and chronic pain.

[60] Another embodiment of the present invention provides the method of embodiment [31] wherein the pain associated with depression comprises atypical depression and chronic pain and wherein the chronic pain precedes the atypical depression.

[61] Another embodiment of the present invention provides the method of embodiment [31] wherein the pain associated with depression comprises atypical depression and chronic pain and wherein the atypical depression precedes the chronic pain.

[62] Another embodiment of the present invention provides the method of any one of embodiments [30]-[31] wherein the pain comprises chronic pain selected from the group of lower back pain, atypical chest

pain, headache, pelvic pain, myofascial face pain, abdominal pain, and neck pain or is chronic pain caused by a disease or condition selected from the group of arthritis, temporal mandibular joint dysfunction syndrome, traumatic spinal cord injury, multiple sclerosis, irritable bowel syndrome, chronic fatigue syndrome, premenstrual syndrome, multiple chemical sensitivity, hyperventilation, closed head injury, fibromyalgia, rheumatoid arthritis, diabetes, cancer, HIV, and interstitial cystitis.

[63] Another embodiment of the present invention provides the method of embodiment [31] wherein the pain comprises atypical depression and neuropathic pain.

[64] Another embodiment of the present invention provides the method of embodiment [31] wherein the pain associated with depression comprises atypical depression that comprises mood reactivity and two or more neurovegetative symptoms selected from the group of hypersomnia, increased appetite or weight gain, leaden paralysis, and a long standing pattern of extreme sensitivity to perceived interpersonal rejection; wherein the neurovegetative symptoms are present for more than about two weeks.

[65] Another embodiment of the present invention provides the method of any one of embodiments [26]-[31] wherein the compound is adjunctively administered with an antidepressant, an analgesic, a muscle

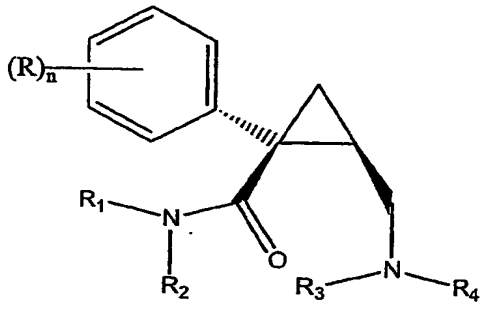
relaxant, an anorectic, a stimulant, an antiepileptic drug, a sedative, a hypnotic, or a combination thereof.

[66] Another embodiment of the present invention provides the method of any one of embodiments [26]-[31] wherein the compound is adjunctively administered with neurontin, pregabalin, pramipexole, l-DOPA, amphetamine, tizanidine, clonidine, tramadol, morphine, codeine, carbamazepine, sibutramine, amphetamine, valium, or trazodone.

[67] Another embodiment of the present invention provides a pharmaceutical composition comprising:

(a) a pharmaceutically acceptable carrier and

(b) an effective anti-chronic fatigue syndrome (CFS) amount, an anti-chronic fatigue syndrome (CFS) associated with depression amount, a dual anti-chronic fatigue syndrome (CFS) and anti-fibromylagia syndrome (FMS) amount, an anti-fibromylagia syndrome (FMS) associated with depression amount, an anti-pain amount, and/or an anti-pain associated with depression amount of a compound of formula (I):



(I)

or sterioisomeric forms, mixtures of sterioisomeric forms, or pharmaceutically acceptable salts thereof wherein,

R is independently hydrogen, halo, alkyl, substituted alkyl, alkoxy, substituted alkoxy, hydroxy, nitro, amino, or substituted amino;

n is 1 or 2;

R_1 and R_2 are each independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, alkaryl, substituted alkaryl, heteroaryl, substituted heteroaryl, heterocycle, or substituted heterocycle; or

R_1 and R_2 can form a heterocycle, substituted heterocycle, heteroaryl, or substituted heteroaryl with the adjacent nitrogen atom;

R_3 and R_4 are each independently hydrogen, alkyl, or substituted alkyl; or

R_3 and R_4 can form a heterocycle, substituted heterocycle, heteroaryl, or substituted heteroaryl with the adjacent nitrogen atom.

[68] Another embodiment of the present invention provides a pharmaceutical composition comprising:

(a) a pharmaceutically acceptable carrier and

(b) an effective anti-chronic fatigue syndrome (CFS) amount, an anti-chronic fatigue syndrome (CFS) associated with depression amount, a dual anti-chronic fatigue syndrome (CFS) and anti-fibromylagia syndrome (FMS) amount, an anti-fibromylagia syndrome (FMS) associated with depression amount, an anti-pain amount, and/or an anti-pain associated with depression amount of milnacipran.

[69] Another embodiment of the present invention provides a pharmaceutical composition comprising:

(a) a pharmaceutically acceptable carrier and

(b) an effective anti-chronic fatigue syndrome (CFS) amount, an anti-chronic fatigue syndrome (CFS) associated with depression amount, a dual anti-chronic fatigue syndrome (CFS) and anti-fibromylagia syndrome (FMS) amount, an anti-fibromylagia syndrome (FMS) associated with depression amount, an anti-pain amount, and/or an anti-pain associated with depression amount of milnacipran (about 25 mg/day to about 250 mg/day).

[70] Another embodiment of the present invention provides a pharmaceutical composition comprising:

(a) a pharmaceutically acceptable carrier,

(b) an effective anti-chronic fatigue syndrome (CFS) amount, an anti-chronic fatigue syndrome (CFS) associated with depression amount, a dual anti-chronic

fatigue syndrome (CFS) and anti-fibromylagia syndrome (FMS) amount, an anti-fibromylagia syndrome (FMS) associated with depression amount, an anti-pain amount, and/or an anti-pain associated with depression amount of milnacipran, and

(c) at least one of an antidepressant, an analgesic, a muscle relaxant, an anorectic, a stimulant, an antiepileptic drug, a sedative, and a hypnotic.

Formulation and Routes of Administration

The NE 5-HT SNRI compounds useful in the present invention, or pharmaceutically acceptable salts thereof, can be delivered to a patient using a wide variety of routes or modes of administration. Suitable routes of administration include, but are not limited to, inhalation, transdermal, oral, rectal, transmucosal, intestinal and parenteral administration, including intramuscular, subcutaneous and intravenous injections.

The term "pharmaceutically acceptable salt" means those salts which retain the biological effectiveness and properties of the compounds used in the present invention, and which are not biologically or otherwise undesirable. Such salts may be prepared from inorganic and organic bases. Salts derived from inorganic bases include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary,

secondary and tertiary amines, substituted amines including naturally-occurring substituted amines, and cyclic amines, including isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, tromethamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, N-alkylglucamines, theobromine, purines, piperazine, piperidine, and N-ethylpiperidine. It should also be understood that other carboxylic acid derivatives would be useful in the practice of this invention, for example carboxylic acid amides, including carboxamides, lower alkyl carboxamides, di(lower alkyl) carboxamides, and the like.

The compounds, or pharmaceutically acceptable salts thereof, may be administered singly, in combination with other NE 5-HT SNRI compounds, and/or in cocktails combined with other therapeutic agents. Of course, the choice of therapeutic agents that can be co-administered with the compounds of the invention will depend, in part, on the condition being treated.

The active NE 5-HT SNRI compounds (or pharmaceutically acceptable salts thereof) may be administered *per se* or in the form of a pharmaceutical composition wherein the active compound(s) is in admixture or mixture with one or more pharmaceutically acceptable carriers, excipients or diluents. Pharmaceutical compositions for use in accordance with

the present invention may be formulated in conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen.

For injection, the NE 5-HT SNRI compounds may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

For oral administration, the compounds can be formulated readily by combining the active compound(s) with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained as a solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol;

cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

Dragee cores can be provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

For administration orally, the compounds may be formulated as a sustained release preparation. Numerous techniques for formulating sustained release preparations are described in the following references - U.S. Patent Nos. 4,891,223; 6,004,582; 5,397,574; 5,419,917; 5,458,005; 5,458,887; 5,458,888; 5,472,708; 6,106,862; 6,103,263; 6,099,862; 6,099,859; 6,096,340; 6,077,541; 5,916,595; 5,837,379; 5,834,023; 5,885,616; 5,456,921; 5,603,956; 5,512,297; 5,399,362; 5,399,359; 5,399,358; 5,725,883; 5,773,025; 6,110,498; 5,952,004;

5,912,013; 5,897,876; 5,824,638; 5,464,633; 5,422,123; and 4,839,177; and WO 98/47491. Specifically, sustained release formulations of milnacipran are described in WO 98/08495. These references are hereby incorporated herein by reference in their entireties.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for such administration.

For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

For administration by inhalation, the active compound(s) may be conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane,

carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g. gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

The compounds may be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the

solubility of the compounds to allow for the preparation of highly concentrated solutions.

Alternatively, the active compound(s) may be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation or transcutaneous delivery (for example subcutaneously or intramuscularly), intramuscular injection or a transdermal patch. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

The pharmaceutical compositions also may comprise suitable solid or gel phase carriers or excipients. Examples of such carriers or excipients include but are not limited to calcium carbonate, calcium phosphate, various sugars, starches, cellulose

derivatives, gelatin, and polymers such as polyethylene glycols.

Effective Dosages

Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredient is contained in a therapeutically or prophylactically effective amount, i.e., in an amount effective to achieve therapeutic or prophylactic benefit, as previously discussed. Of course, the actual amount effective for a particular application will depend, inter alia, on the condition being treated and the route of administration. Determination of an effective amount is well within the capabilities of those skilled in the art, especially in light of the disclosure herein.

Therapeutically effective amounts for use in humans can be determined from animal models. For example, a dose for humans can be formulated to achieve circulating concentration that has been found to be effective in animals. Useful animal models of pain are well known in the art. Models of neuropathic pain are described in Zeltser et al., 2000, *Pain* 89:19-24; Bennett et al., 1988, *Pain* 33:87-107; Seltzer et al., 1990, *Pain* 43:205-218; Kim et al., 1992, *Pain* 50:355-363; and Decosterd et al., 2000, *Pain* 87:149-158. An animal model of inflammatory pain using complete Freund's adjuvant is described in Jasmin et al., 1998, *Pain* 75: 367-382. The stress-induced hyperalgesia model described in Quintero et

al., 2000, *Pharmacology, Biochemistiy and Behavior* 67:449-458 may be used as an animal model of FMS and CFS.

Effective amounts for use in humans can be also be determined from human data for the NE 5-HT SNRI compounds used to treat depression. The amount administered can be the same amount administered to treat depression or can be an amount lower than the amount administered to treat depression. For example, the amount of milnacipran administered to treat depression is in the range of about 50 mg - 400 mg/day. Thus, either 50 mg - 400 mg/day or a lower dose can be administered for practicing the present invention.

Patient doses for oral administration of the NE 5-HT SNRT compound typically range from about 1 μg - 1 gm/day. For example, for the treatment of FMS, CFS, or pain with milnacipran the dosage range is typically from 25 mg - 400 mg/day, more typically from 100 mg - 250 mg/day. The dosage may be administered once per day or several or multiple times per day. The amount of the NE 5-HT SNRI compound administered to practice methods of the present invention will of course, be dependent on the subject being treated, the severity of the affliction, the manner of administration and the judgment of the prescribing physician. The dose used to practice the invention can produce the desired therapeutic or prophylactic effects, without producing serious side effects.

EXAMPLES

EXAMPLE 1: ASSESSMENT OF THE ANALGESIC PROPERTIES OF MILNACIPRAN IN A RAT PAIN MODEL

The rats used in this study are divided into two groups. One group of rats receive a spinal ligation as described in Kim et al., 1992, *Pain* 50(3):355-63 and the other group of rats receive a sham surgery. Each group of rats is further divided into 5 subgroups. Each subgroup receives subcutaneous injection of the vehicle or one of the 4 test doses of milnacipran (5, 10, 25, and 50 mg/kg). The vehicle or milnacipran are administered at a pre-determined time point following the surgeries. Allodynia and thermal hyperalgesia are respectively measured with Von Frey filaments and tail- or paw-flick with a radiant heat source. The allodynia and thermal hyperalgesia measurements are performed at the following time points - prior to surgery, following surgery but prior to the administration of vehicle or milnacipran, and following surgery after the administration of vehicle or milnacipran. The allodynia and thermal hyperalgesia measurements will provide information on the ability of milnacipran to block the development of mechanical allodynia and thermal hyperalgesia.

EXAMPLE 2: ASSESSMENT OF THE EFFICACY OF MILNACIPRAN IN AN FMS ANIMAL MODEL

This study is performed on rats or mice that have undergone stress-induced hyperalgesia as described in Quintero et al., 2000, *Pharmacology, Biochemistry and*

Behavior 67:449-458. The study consists of 3 groups: placebo, milnacipran subcutaneous pretreatment, and milnacipran treatment. The milnacipran groups are further divided to 4 subgroups and each subgroup is administered 5, 10, 25, or 50 mg/kg of milnacipran. In the milnacipran subcutaneous pretreatment group, the milnacipran is administered prior to the inducement of the stress-induced hyperalgesia. In the milnacipran treatment group, the milnacipran is administered following the inducement of the stress-induced hyperalgesia. Allodynia and thermal hyperalgesia are respectively measured with Von Frey filaments and tail- or paw-flick with a radiant heat source. The allodynia and thermal hyperalgesia measurements are performed at the following time points - prior to both the inducement of stress-induced hyperalgesia and the administration of the milnacipran, prior to the inducement of stress-induced hyperalgesia but following the administration of the milnacipran, following the inducement of stress-induced hyperalgesia but prior to administration of the milnacipran, following both the inducement of stress-induced hyperalgesia and the administration of the milnacipran. The allodynia and thermal hyperalgesia measurements provide information on whether pretreatment or treatment with milnacipran will be effective in the treatment of stress-induced thermal and mechanical hyperalgesia.

EXAMPLE 3: ASSESSMENT OF THE EFFICACY OF MILNACIPRAN IN FMS PATIENTS

Approximately 40 subjects are studied for a total of 6 weeks, after being weaned from their previous analgesic or antidepressant medications.

The inclusion criteria for this study is as follows:

1. Patients meet the 1990 American College of Rheumatology criteria for fibromyalgia syndrome.

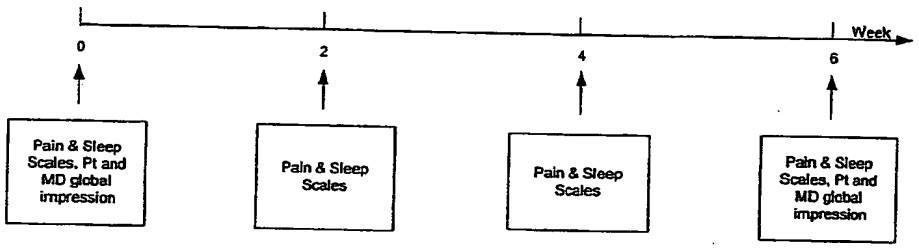
2. Male or female between the ages of 18 and 70 years. Females are either postmenopausal (no menses for at least 1 year) or status-post oophorectomy (bilateral) or have a negative pregnancy test and be using an accepted method of contraception.

3. Patients have a Gracely intensity pain scale recording (weekly recall) of at least 10 or more on a 20 point scale at baseline.

4. Patients may use non-prescription doses of NSAIDs, aspirin and acetaminophen on a PRN basis for acute pain unrelated to their underlying fibromyalgia.

The patients are divided into 2 groups. The first group is administered 100mg of milnacipran in a single-dose in the morning, while the second group is administered 50mg twice a day (i.e., upon awakening

and prior to going to sleep). Each patient is then followed for 6 weeks, with visits every two weeks, as follows:



As indicated above, global patient (Pt) and physician (MD) assessments are taken at the beginning and end of the trial. In addition, a total of 4 sets of pain and sleep measures are also performed at 2-week intervals. The pain measure consists of the patient's recall of overall pain over the previous 2-week period as indicated by a 10cm visual analog scale. The sleep instrument consists of 4 questions taken from the Jenkin's sleep questionnaire. It is expected that milnacipran will produce an improvement in a majority of the patients.

EXAMPLE 4: ASSESSMENT OF THE EFFICACY OF MILNACIPRAN IN PATIENTS WITH PAINFUL DIABETIC NEUROPATHY

20 patients with painful diabetic neuropathy (DN) are studied in a double-blind cross-over study. The inclusion criteria for the study are - age of between 18 and 85 years, daily pain of at least "moderate intensity" on the Gracely scale for greater than three months that was present more than 50% of the day, and

adequate communication ability demonstrated during a telephone conversation and by completion of a pain diary. Additional inclusion criteria are a diagnosis of diabetes, and distal, symmetrical diabetic neuropathy as assessed by either an unequivocal decrease in pinprick, temperature, or vibration sense in both feet or ankles or decreased or absent ankle jerk reflexes. Exclusion criteria are the presence of another more painful condition, difficulty with ambulation, any unstable disease process, a history of significant substance abuse or alcoholism, liver or kidney disease, or concurrent use of a monoamine oxidase inhibitor.

Milnacipran is compared to placebo in a randomized, double-blind, two-period, crossover study. After discontinuing other medication for pain for two weeks, patients enter a one-week baseline period, followed by two six-week drug treatment periods, separated and concluded by a one-week washout period. The treatments, given in random order, are milnacipran titrated up to maximum tolerated dose or placebo. A nurse calls the patients every three days to titrate medication dosage and to assess pain, side effects, and study compliance. During the first four weeks of each period (titration phase) the medication is increased by 25 mg/day every three days unless the patient reports complete pain relief, side effects that interfere with daily activities, or unless the maximum dose of 200 mg daily is reached. During weeks

5 and 6 (maintenance phase), the highest well-tolerated dose is maintained at a constant level.

Prior to randomization, a general physical exam and laboratory tests (complete blood count, liver function tests, blood glucose, hemoglobin Alc, blood urea nitrogen, creatinine, electrolytes and urinalysis) is obtained. Diabetics are examined to assure they had adequate blood sugar control before and during the trial. They are instructed to perform daily blood sugar monitoring using a fingerstick and a home glucometer. In addition, a neurologic examination is performed at baseline to identify any area of increased pain to pinprick (hyperalgesia), decreased sensation to pinprick, or pain with stimulation by cotton gauze (allodynia); these studies are conducted every 2 weeks during the trial. In addition, patients record their pain intensity in a diary 3 times daily using the Gracely scale. It is expected that milnacipran will produce an improvement in the majority of patients, as measured by both physician neurological exam and patient diary.

Each of the patent applications, patents, publications, and other published documents mentioned or referred to in this specification is herein incorporated by reference in its entirety, to the same extent as if each individual patent application, patent, publication, and other published document was specifically and individually indicated to be incorporated by reference.

While the present invention has been described with reference to the specific embodiments thereof, it should be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing from the true spirit and scope of the invention. In addition, many modifications may be made to adapt a particular situation, material, composition of matter, process, process step or steps, to the objective, spirit and scope of the present invention. All such modifications are intended to be within the scope of the claims appended hereto.

Claims

What is claimed is:

1. The use of a selective norepinephrine (NE) - serotonin (5-HT) reuptake inhibitor (NSRI) for the manufacture of a medicament useful for treating chronic fatigue syndrome (CFS) in a mammal.

2. The use of a selective norepinephrine (NE) - serotonin (5-HT) reuptake inhibitor (NSRI) for the manufacture of a medicament useful for treating chronic fatigue syndrome (CFS) that is associated with depression.

3. The use of a selective norepinephrine (NE) - serotonin (5-HT) reuptake inhibitor (NSRI) for the manufacture of a medicament useful for treating a combination of chronic fatigue syndrome (CFS) and fibromylagia syndrome (FMS).

4. The use of a selective norepinephrine (NE) - serotonin (5-HT) reuptake inhibitor (NSRI) for the manufacture of a medicament useful for treating fibromylagia syndrome (FMS) associated with depression.

5. The use of a selective norepinephrine (NE) - serotonin (5-HT) reuptake inhibitor (NSRI) for the manufacture of a medicament useful for treating pain in a mammal.

6. The use of a selective norepinephrine (NE) - serotonin (5-HT) reuptake inhibitor (NSRI) for the manufacture of a medicament useful for treating pain associated with depression.

7. The use of a compound in any one of claims 1-6 wherein the mammal is a human.

8. The use of a compound in any one of claims 1-6 wherein the noradrenergic reuptake inhibitor (NARI) has an IC_{50} for inhibition of noradrenaline reuptake into synaptosomes from mammalian cerebral cortex of 1 micromolar (μM) or less.

9. The use of a compound in any one of claims 1-6 wherein the noradrenergic reuptake inhibitor (NARI) has an IC_{50} for inhibition of noradrenaline reuptake into synaptosomes from mammalian cerebral cortex of 100 nanomolar (nM) or less.

10. The use of a compound in any one of claims 1-6 wherein the selective NSRI has an NE : 5-HT reuptake inhibition ratio of at least about 1.

11. The use of a compound in any one of claims 1-6 wherein the selective NSRI has an NE : 5-HT reuptake inhibition ratio of up to about 20.

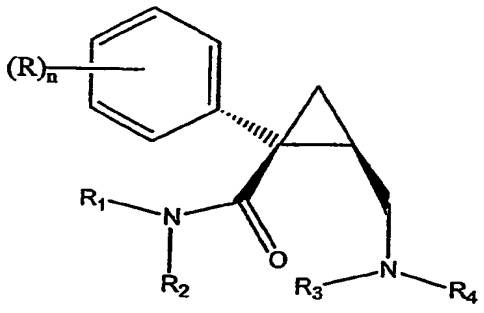
12. The use of a compound in any one of claims 1-6 wherein the selective NSRI has an NE : 5-HT reuptake inhibition ratio of about 1 : 1 to about 20 : 1.

13. The use of a compound in any one of claims 1-6 wherein the selective NSRI has an NE : 5-HT reuptake inhibition ratio of about 1 : 1 to about 5 : 1.

14. The use of a compound in any one of claims 1-6 wherein the selective NSRI has an NE : 5-HT reuptake inhibition ratio of about 1 : 1 to about 3 : 1.

15. The use of a compound in any one of claims 1-6 wherein the selective norepinephrine (NE) - serotonin (5-HT) reuptake inhibitor (NSRI) has limited post-synaptic receptor effects, such that the K_i at each of adrenergic and cholinergic sites is greater than about 500 nanomolar (nM).

16. The use of a compound in any one of claims 1-6 wherein the compound is a compound of formula (I):



(I)

or a sterioisomeric form, a mixture of sterioisomeric forms, or a pharmaceutically acceptable salt thereof wherein,

R is independently hydrogen, halo, alkyl, substituted alkyl, alkoxy, substituted alkoxy, hydroxy, nitro, amino, or substituted amino;

n is 1 or 2;

R_1 and R_2 are each independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, alkaryl, substituted alkaryl, heteroaryl, substituted heteroaryl, heterocycle, or substituted heterocycle; or

R_1 and R_2 can form a heterocycle, substituted heterocycle, heteroaryl, or substituted heteroaryl with the adjacent nitrogen atom;

R_3 and R_4 are each independently hydrogen, alkyl, or substituted alkyl; or

R_3 and R_4 can form a heterocycle, substituted heterocycle, heteroaryl, or substituted heteroaryl with the adjacent nitrogen atom.

17. The use of a compound in claim 16 wherein R is hydrogen.

18. The use of a compound in claim 16 wherein n is 1.

19. The use of a compound in claim 16 wherein R_1 is alkyl.

20. The use of a compound in claim 16 wherein R_1 is ethyl.

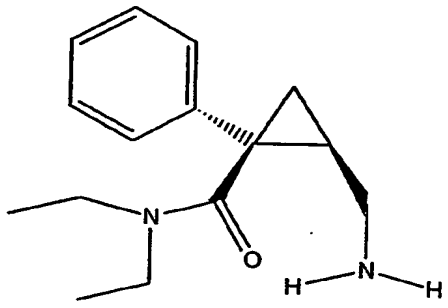
21. The use of a compound in claim 16 wherein R_2 is alkyl.

22. The use of a compound in claim 16 wherein R_2 is ethyl.

23. The use of a compound in claim 16 wherein R_3 is hydrogen.

24. The use of a compound in claim 16 wherein R_4 is hydrogen.

25. The use of a compound in claim 16 wherein the compound is (milnacipran) a compound of the formula:



or a sterioisomeric form, a mixture of sterioisomeric forms, or a pharmaceutically acceptable salt thereof.

26. The use of a compound in claim 25 wherein the compound of the formula recited therein (milnacipran) is administered up to about 400 mg/day.

27. The use of a compound in claim 25 wherein the compound of the formula recited therein (milnacipran) is administered in about 25 mg/day to about 250 mg/day.

28. The use of a compound in claim 25 wherein the compound of the formula recited therein (milnacipran) is administered one or more (e.g., 1, 2, 3, 4, or 5) times per day.

29. The use of a compound in any one of claims 1-3 wherein the chronic fatigue syndrome (CFS) is accompanied by the physiological symptoms selected from weakness, muscle aches and pains, excessive sleep, malaise, fever, sore throat, tender lymph nodes, impaired memory and/or mental concentration, insomnia, disordered sleep, localized tenderness, diffuse pain and fatigue, and combinations thereof.

30. The use of a compound in any one of claims 3-4 wherein the fibromylagia syndrome (FMS) is accompanied by the physiological symptoms selected from a generalized heightened perception of sensory stimuli, abnormalities in pain perception in the form of allodynia (pain with innocuous stimulation), abnormalities in pain perception in the form of hyperalgesia (increased sensitivity to painful stimuli), and combinations thereof.

31. The use of a compound in claim 4 wherein the fibromylagia syndrome (FMS) associated with depression comprises fibromylagia syndrome (FMS) and atypical depression.

32. The use of a compound in claim 4 wherein the fibromylagia syndrome (FMS) associated with depression comprises fibromylagia syndrome (FMS) and atypical depression, and wherein the fibromylagia syndrome (FMS) precedes the atypical depression.

33. The use of a compound in claim 4 wherein the fibromylagia syndrome (FMS) associated with depression comprises fibromylagia syndrome (FMS) and atypical depression, and wherein the atypical depression precedes the fibromylagia syndrome (FMS).

34. The use of a compound in claim 6 wherein the pain associated with depression comprises atypical depression and chronic pain.

35. The use of a compound in claim 6 wherein the pain associated with depression comprises atypical depression and chronic pain and wherein the chronic pain precedes the atypical depression.

36. The use of a compound in claim 6 wherein the pain associated with depression comprises atypical depression and chronic pain and wherein the atypical depression precedes the chronic pain.

37. The use of a compound in any one of claims 5-6 wherein the pain comprises chronic pain selected from the group of lower back pain, atypical chest pain, headache, pelvic pain, myofascial face pain, abdominal pain, and neck pain or is chronic pain caused by a disease or condition selected from the group of arthritis, temporal mandibular joint dysfunction syndrome, traumatic spinal cord injury, multiple sclerosis, irritable bowel syndrome, chronic fatigue syndrome, premenstrual syndrome, multiple chemical sensitivity, hyperventilation, closed head injury, fibromyalgia, rheumatoid arthritis, diabetes, cancer, HIV, and interstitial cystitis.

38. The use of a compound in claim 6 wherein the pain comprises atypical depression and neuropathic pain.

39. The use of a compound in claim 6 wherein the pain associated with depression comprises atypical depression that comprises mood reactivity and two or more neurovegetative symptoms selected from the group of hypersomnia, increased appetite or weight gain, leaden paralysis, and a long standing pattern of extreme sensitivity to perceived interpersonal rejection; wherein the neurovegetative symptoms are present for more than about two weeks.

40. The use of a compound in any one of claims 1-6 wherein the compound is adjunctively administered with an antidepressant, an analgesic, a muscle relaxant, an

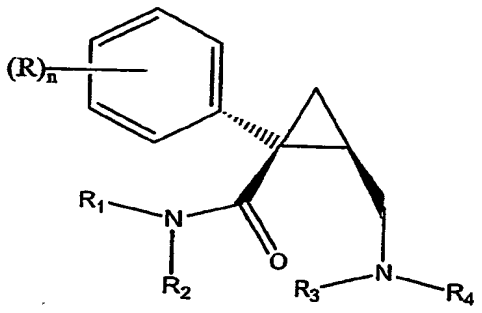
anorectic, a stimulant, an antiepileptic drug, a sedative, a hypnotic, or a combination thereof.

41. The use of a compound in any one of claims 1-6 wherein the compound is adjunctively administered with neurontin, pregabalin, pramipexole, l-DOPA, amphetamine, tizanidine, clonidine, tramadol, morphine, codeine, carbamazepine, sibutramine, amphetamine, valium, or trazodone.

42. A pharmaceutical composition comprising:

(a) a pharmaceutically acceptable carrier and

(b) an effective anti-chronic fatigue syndrome (CFS) amount, an anti-chronic fatigue syndrome (CFS) associated with depression amount, a dual anti-chronic fatigue syndrome (CFS) and anti-fibromylagia syndrome (FMS) amount, an anti-fibromylagia syndrome (FMS) associated with depression amount, an anti-pain amount, and/or an anti-pain associated with depression amount of a compound of formula (I):



(I)

or sterioisomeric forms, mixtures of sterioisomeric forms, or pharmaceutically acceptable salts thereof wherein,

R is independently hydrogen, halo, alkyl, substituted alkyl, alkoxy, substituted alkoxy, hydroxy, nitro, amino, or substituted amino;

n is 1 or 2;

R_1 and R_2 are each independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, alkaryl, substituted alkaryl, heteroaryl, substituted heteroaryl, heterocycle, or substituted heterocycle; or

R_1 and R_2 can form a heterocycle, substituted heterocycle, heteroaryl, or substituted heteroaryl with the adjacent nitrogen atom;

R_3 and R_4 are each independently hydrogen, alkyl, or substituted alkyl; or

R_3 and R_4 can form a heterocycle, substituted heterocycle, heteroaryl, or substituted heteroaryl with the adjacent nitrogen atom.

43. A pharmaceutical composition comprising:

(a) a pharmaceutically acceptable carrier and

(b) an effective anti-chronic fatigue syndrome (CFS) amount, an anti-chronic fatigue syndrome (CFS) associated with depression amount, a dual anti-chronic fatigue syndrome (CFS) and anti-fibromylagia syndrome (FMS) amount, an anti-fibromylagia syndrome (FMS) associated with depression amount, an anti-pain amount, and/or an anti-pain associated with depression amount of milnacipran.

44. A pharmaceutical composition comprising:

(a) a pharmaceutically acceptable carrier and

(b) an effective anti-chronic fatigue syndrome (CFS) amount, an anti-chronic fatigue syndrome (CFS) associated with depression amount, a dual anti-chronic fatigue syndrome (CFS) and anti-fibromylagia syndrome (FMS) amount, an anti-fibromylagia syndrome (FMS) associated with depression amount, an anti-pain amount, and/or an anti-pain associated with depression amount of milnacipran (about 25 mg/day to about 250 mg/day).

45. A pharmaceutical composition comprising:

(a) a pharmaceutically acceptable carrier,

(b) an effective anti-chronic fatigue syndrome (CFS) amount, an anti-chronic fatigue syndrome (CFS) associated with depression amount, a dual anti-chronic fatigue syndrome (CFS) and anti-fibromylagia syndrome (FMS) amount, an anti-fibromylagia syndrome (FMS) associated with depression amount, an anti-pain amount, and/or an anti-pain associated with depression amount of milnacipran, and

(c) at least one of an antidepressant, an analgesic, a muscle relaxant, an anorectic, a stimulant, an antiepileptic drug, a sedative, and a hypnotic.

INTERNATIONAL SEARCH REPORT

Inter ial Application No
PCT/US 02/35396

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K45/00 A61K31/165 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, MEDLINE, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	WO 99 59593 A (TOLLEFSON GARY DENNIS :LILLY CO ELI (US); MICHELSON DAVID (US)) 25 November 1999 (1999-11-25) page 6, line 10 page 9, line 5 - line 21 page 11, line 29 - line 31	1-40, 42-45
	EP 0 759 299 A (LILLY CO ELI) 26 February 1997 (1997-02-26) page 15, line 20 - line 42; claims	1-40
X Y	WO 00 32178 A (MUELLER PETER STERLING) 8 June 2000 (2000-06-08) claims; example 17	1-15, 29-39 1-41
X	WO 97 35584 A (LILLY CO ELI) 2 October 1997 (1997-10-02) page 2, line 5 -page 3, line 5; claims	5-15, 34-40

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 February 2003	28/02/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Winger, R

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/35396

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	NUTT D AND JOHNSON F N: "Potential Applications of Venlafaxine" REV. CONTEMP. PHARMACOTHER., vol. 9, 1998, pages 321-331, XP001145445 page 324 page 328 -page 329	1-15
P,X	RAO SRINIVAS G: "The neuropharmacology of centrally-acting analgesic medications in fibromyalgia." RHEUMATIC DISEASE CLINICS OF NORTH AMERICA, vol. 28, no. 2, May 2002 (2002-05), pages 235-259, XP009005801 ISSN: 0889-857X page 244 -page 247; table 1	3-39
X	DWIGHT M M ET AL: "An open clinical trial of venlafaxine treatment of fibromyalgia." PSYCHOSOMATICS. UNITED STATES 1998 JAN-FEB, vol. 39, no. 1, January 1998 (1998-01), pages 14-17, XP009005796 ISSN: 0033-3182 abstract; table 2	3-15
X	NINAN P T: "Use of venlafaxine in other psychiatric disorders." DEPRESSION AND ANXIETY. UNITED STATES 2000, vol. 12 Suppl 1, 2000, pages 90-94, XP009005799 ISSN: 1091-4269 page 92 -page 93	3-15
X	US 4 478 836 A (MOUZIN GILBERT ET AL) 23 October 1984 (1984-10-23) cited in the application column 1; claim 11	42-44
X	FR 2 752 732 A (PF MEDICAMENT) 6 March 1998 (1998-03-06) claims 1,2; examples	42-44
P,Y	WO 02 053140 A (PHARMACIA AB ;SVENSSON TORGNY (SE); WONG ERIK HO FONG (US); UPJOHN) 11 July 2002 (2002-07-11) claims 1,2,11	1-41
Y	WO 01 26623 A (LAXDALE LTD) 19 April 2001 (2001-04-19) cited in the application page 1, line 25; claim 1	1-41

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-15, 29-41 (in part)

Present claims 1-15 and 29-41 relate to a compound defined by reference to a desirable characteristic or property, namely selective norepinephrine serotonin reuptake inhibition.

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds of formula I and the common SNRIs defined on page 11.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/35396

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-15, 29-41 (in part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter ›nal Application No
PCT/US 02/35396

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9959593 A	25-11-1999	AU 3891299 A	06-12-1999
		EP 1077704 A1	28-02-2001
		JP 2002515435 T	28-05-2002
		WO 9959593 A1	25-11-1999
EP 0759299 A	26-02-1997	AT 192042 T	15-05-2000
		AU 6776196 A	12-03-1997
		DE 69607904 D1	31-05-2000
		DE 69607904 T2	05-10-2000
		DK 759299 T3	07-08-2000
		EP 0759299 A1	26-02-1997
		ES 2145977 T3	16-07-2000
		GR 3034007 T3	30-11-2000
		PT 759299 T	29-09-2000
		WO 9706792 A1	27-02-1997
WO 0032178 A	08-06-2000	US 6323242 B1	27-11-2001
		AU 1748800 A	19-06-2000
		EP 1135115 A2	26-09-2001
		US 2002137798 A1	26-09-2002
		WO 0032178 A2	08-06-2000
WO 9735584 A	02-10-1997	AU 2587297 A	17-10-1997
		CA 2250042 A1	02-10-1997
		EP 0906104 A1	07-04-1999
		JP 2000507544 T	20-06-2000
		WO 9735584 A1	02-10-1997
		US 2003013689 A1	16-01-2003
		US 6444665 B1	03-09-2002
US 4478836 A	23-10-1984	FR 2508035 A1	24-12-1982
		AT 13422 T	15-06-1985
		AU 550774 B2	10-04-1986
		AU 8508682 A	06-01-1983
		CA 1202639 A1	01-04-1986
		DE 3263734 D1	27-06-1985
		EP 0068999 A1	05-01-1983
		ES 8303293 A1	01-05-1983
		JP 1477542 C	27-01-1989
		JP 58004752 A	11-01-1983
		JP 63023186 B	16-05-1988
		LU 90410 A9	31-08-1999
		ZA 8204453 A	27-04-1983
FR 2752732 A	06-03-1998	FR 2752732 A1	06-03-1998
		AT 213629 T	15-03-2002
		AU 727018 B2	30-11-2000
		AU 4121297 A	19-03-1998
		BR 9711378 A	17-08-1999
		CN 1232387 A	20-10-1999
		DE 69710757 D1	04-04-2002
		DK 939626 T3	27-05-2002
		EP 0939626 A1	08-09-1999
		ES 2171991 T3	16-09-2002
		WO 9808495 A1	05-03-1998
		JP 2000516946 T	19-12-2000
		PT 939626 T	31-07-2002

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 02/35396

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 02053140 A	11-07-2002	WO 02053140 A2	11-07-2002
		US 2002156067 A1	24-10-2002
WO 0126623 A	19-04-2001	GB 2355191 A	18-04-2001
		AU 7932800 A	23-04-2001
		EP 1220689 A2	10-07-2002
		WO 0126623 A2	19-04-2001
		NO 20021716 A	10-06-2002
		SK 4672002 A3	10-09-2002
		US 6441038 B1	27-08-2002